REMARKS

In the instant Action, claims 1-18 and 20-25 are listed as pending. Claims 18 and 21-25 are listed as withdrawn. Claims 1-17 and 20 are rejected, however the Examiner has indicated that claims 14-17 would be allowable if rewritten to overcome the objections and rejections presented in the instant Action.

Applicant's acknowledge with appreciation the Examiner's determination that the elected species is free of the prior art, and the Examiner's expansion of the search to the compounds of Claims 14-17, which the Examiner has also found to be free of the art.

Claim 1 is amended herein to define Z as an analog of somatostatin, LHRH or bombesin. Support for this amendment is found in claims 9 and 10-12 as originally filed.

Claim 1 is also amended so as to define B^{1-4} such that at least one of B^{1-4} is -(C(O)-A1-A2-A3-A4-A5-C(O))s-. Support for this amendment is found in paragraphs [0009] and [0101] which indicate that the cytotoxic or cytostatic moiety of the compounds of the invention are joined with a ligand moiety via a linker, *i.e.*, B^1, B^2, B^3 or B^4. Compounds lacking at least one of B^1, B^2, B^3 or B^4 would fail to contain the linker feature described in [0009] and [0101] and shown in Formula I of claim 1. Additional support for this amendment is found in the compounds of the invention itself as all compounds include at least one -(C(O)-A1-A2-A3-A4-A5-C(O))s- moiety. Further support for this amendment to claim 1 is found by inspection of the definition of camptothecin, paclitaxel and doxorubicin presented in paragraphs [0125] to [0129], each of which lack the -(C(O)-A1-A2-A3-A4-A5-C(O))s- moiety, and the compounds prepared by Applicants (Tables A – I), each of which include both a cytotoxic or cytostatic moiety (such as camptothecin, paclitaxel or doxorubicin) and a -(C(O)-A1-A2-A3-A4-A5-C(O))s- moiety. Lastly, additional support for this amendment is found in the compounds of claims 14-17, each of which contains a -(C(O)-A1-A2-A3-A4-A5-C(O))s- moiety and which the Examiner has deemed to recite allowable subject matter over the art.

Claims 2 and 3 are amended to address punctuation issues. Claims 2-15 are amended to recite "The compound" in place of "A compound". Claim 9 is canceled as the limitations of this claim are incorporated into claim 1. Claims 14, 15 and 18 are amended to include SEQ ID NOs

for selected compounds. Claims 14-17 are amended to address the Examiner's concerns regarding dependent claim format.

OBJECTIONS TO THE SPECIFICATION

On pages 4 and 5-6 of the instant Action, the Examiner objects to the specification, alleging that the specification recites sequences without sequence identifiers. In the present reply, Applicants amend the specification and claims to include SEQ ID NOs for those linear peptide compounds which contain four or more amino acids and do not contain D amino acids.

OBJECTIONS TO THE CLAIMS

On pages 4-5 of the instant Action, the Examiner objects to claims 2-15 for various informalities:

Claims 2 and 3: The Examiner objects to claims 2 and 3 for containing an extra period at the end of each claim. Applicants have amended these claims to address this allegation.

Claims 2-15: The Examiner objects to claims 2-15 for reciting "The compound" rather than "A compound". Applicants have amended these claims to address this allegation.

Claim 14: The Examiner objects to claim 14 for reciting peptides that require sequence identifiers. Applicants have amended this claim to address this allegation.

Claims 14-17: The Examiner objects to claims 14-17 as being of improper dependent format for failing to further limit the subject matter of a previous claim. The Examiner alleges that claims 14-17 are broader in scope than the independent claim as claims 14-17 use the term "comprises". Applicants have amended these claims to address this allegation.

REJECTIONS OF THE CLAIMS

1A) Rejection of claims 1-9, 13 and 20 under 35 U.S.C. 112, first paragraph, written description

On pages 6-8 of the instant Action, the Examiner rejects claims 1-9, 13 and 20 as failing to comply with the written description requirement. The Examiner summarizes the rejection on page 7, stating "[f]or Applicant's clarification, the rejection is set forth with regards to the moiety "Z"." The complete details of the Examiner's rejection are found on pages 6-8 of the instant Action and are not reiterated in full in this reply.

1B) Amendments to the claims

Claims 1-8 and 10-18 are currently amended. Claim 9 is cancelled.

1C) Claims 1-8, 13 and 20 fulfill the written description requirement

Claim 9 is cancelled, rendering moot this rejection to this claim.

Applicants respectfully submit that instant claims 1-8, 13 and 20 fulfill the written description requirement. Applicants submit that the amendments presented herein, in which "Z" of claim 1 is defined as an analog of somatostatin, LHRH or bombesin, fully defines the ligand moiety portion of the compounds of the invention. Applicants respectfully submit that this amendment to claim 1 addresses the Examiners' issues regarding this claim as well as dependent claims 2-8, 13 and 20.

1D) Request for the removal of the rejection of claims 1-8, 13 and 20 under 35 U.S.C. first paragraph

Applicants respectfully submit that the amendments proposed herein render claims 1-8, 13 and 20 fully compliant with the written description requirement. Applicants respectfully request the withdrawal of the rejection of claims 1-8, 13 and 20 under 35 U.S.C., first paragraph.

2A) Rejection of claims 1-17 and 20 under 35 U.S.C. 112, second paragraph, indefiniteness

On pages 8-9 of the instant Action, the Examiner rejects original claims 1-17 and 20 as being indefinite for failing to particularly point out and distinctly claims the subject matter which Applicants regard as the invention. The Examiner alleges that "it is unclear how one can independently select Doc, Aepa, etc., when s=1, as there is no requirement in the claim that one must select C(O)-A1…A5-C(O). As such, the claim sets up contradictory requirements, and is indefinite." The complete details of the Examiner's rejection are found on pages 8-9 of the instant Action and are not reiterated in full in this reply.

2B) Amendments to the claims

Claims are amended as previously described.

2C) Claims 1-8, 10-17 and 20 are not indefinite

Claim 9 is cancelled, rendering moot this rejection to this claim.

Applicants respectfully submit that instant claims 1-8, 10-17 and 20 clearly point out the metes and bounds of the claimed invention. Applicants submit that the amendments presented herein clearly define and describe linkers B^1-B^4 of the formula of claim 1.

As recited in the specification at paragraphs [0009] and [0101], as well as shown in the compounds of Tables A-I, the cytotoxic or cytostatic moiety "X" is joined to receptor ligand "Z" via a linker. The linker is represented by B^1-B^4 of the formula of claim 1. Inspection of the compounds of the invention as shown in Tables A-I of the specification and claims 14-17 show that each compound includes a -(C(O)-A1-A2-A3-A4-A5-C(O))$_s$- moiety. Inspection of the cytotoxic and cytostatic moieties as defined on pages 23-25 of the specification and the peptide ligand as defined on pages 5-7 of the specification show that these moieties lack a -(C(O)-A1-A2-A3-A4-A5-C(O))$_s$- group. Thus, at least one of positions B^1-B^4 must be present in a compound of the invention and, as all compounds include a -(C(O)-A1-A2-A3-A4-A5-C(O))$_s$- moiety, claim 1 is amended to recite a compound in which a -(C(O)-A1-A2-A3-A4-A5-C(O))$_s$- group is present at at least one of positions B^1-B^4.

On page 9 of the instant Action, the Examiner alleges that claim 1 is indefinite with regard to the definition of R1 and R2. Applicants submit that the skilled artisan in possession of the specification would be able to create a ring structure using the allowed substitutions for R1 and R2.

Also on page 9 of the instant Action, the Examiner alleges that claims 14-17 lack a clear antecedent basis. Applicants submit that the amendments to instant claims 14-17 address this concern.

2D) Request for the removal of the rejection of claims 1-8, 10-17 and 20 under 35 U.S.C. second paragraph

Applicants respectfully submit that the amendments proposed herein render claims 1-8, 10-17 and 20 definite. Applicants respectfully request the withdrawal of the rejection of claims 1-8, 10-17 and 20 under 35 U.S.C., second paragraph.

3A) Rejection of claims 1-4, 9-13 and 20 under 35 U.S.C. 102(b), anticipation

On pages 9-11 of the instant Action, the Examiner raised four different 102(b) rejections against claims 1-4, 9-13 and 20. The Examiner alleges that claims 1, 2 13 and 20 are anticipated by Fischer (WO 00/01417; refered to hereinafter as "Fischer") and Arap (WO 02/20722; referred to hereinafter as "Arap"), and that claims 1-4, 9-13 and 20 are anticipated by Schally (WO 97/19954; referred to hereinafter as "Schally") and Fuselier (Med. Chem. Lett., 2003, 10:799-803; referred to hereinafter as "Fuselier"). The complete details of the Examiner's rejection are found on pages 9-11 of the instant Action and are not reiterated in full in this reply.

3B) Amendments to the claims

Claims are amended as previously described.

3C) Claims 1-4, 10-13 and 20 are novel and not anticipated

Claim 9 is cancelled, rendering moot this rejection to this claim.

Applicants respectfully submit that claims 1, 2, 13 and 20 are novel and not anticipated by Fischer or Arap. Fischer and Arap each fail to disclose compounds containing a C(O)-A1…A5-C(O) linker and somatostatin, LHRH or bombesin peptide ligands.

Applicants respectfully submit that claims 1-4, 10-13 and 20 are novel and not anticipated by Schally or Fuselier. Instant claim 1 not only requires the presence of a -(C(O)-A1-A2-A3-A4-A5-C(O))$_s$- moiety, claim 1 also sets forth the requirement that when "X" is doxorubicin or an analog of doxorubicin, the compound must also contain Doc and/or Aepa moieties ("when X is doxorubicin or a doxorubicin derivative, at least one of m and n is not 0"). Schally and Fuselier each fails to disclose compounds which meet these requirements.

3D) Request for the removal of the rejection of claims 1-4, 10-13 and 20 over Fischer, Schally, Fuselier and Arap

Applicants respectfully submit that the amendments proposed herein render claims 1-4, 10-13 and 20 novel and not anticipated by Fischer, Shally, Fuslier or Arap. Applicants respectfully request the withdrawal of the rejection of claims 1-4, 10-13 and 20 under 35 U.S.C. 102(b).

4A) Rejection of claims 1-13 and 20 under 35 U.S.C. 103(a), obviousness

On pages 11-13 of the instant Action, the Examiner rejects claims 1-13 and 20 as being obvious over Fischer in light of Schally. The Examiner alleges that Fischer teaches drug-carrier conjugates including "a variety of linker moieties". The Examiner alleges that one would have been motivated to use the LHRH, somatostatin or bombesin peptides disclosed by Schally joined with the linker and drug combination of Fischer to generate the compounds of the instant invention. The complete details of the Examiner's rejection are found on pages 11-13 of the instant Action and are not reiterated in full in this reply.

4B) Amendments to the claims

Claims are amended as previously described.

4C) Claims 1-8, 10-13 and 20 are not obvious in light of the art

Claim 9 is cancelled, rendering moot this rejection to this claim.

Applicants respectfully submit that instant claims 1-8, 10-13 and 20 are not obvious in light of the teachings of Fischer combined with Schally.

Inspection of the data provided by Fischer clearly suggests that the presence of a succinyl-type linker detracts from the efficacy of a drug-linker-carrier combination. Applicants respectfully direct the Examiner to Tables 1, 2 and 3 on pages 65-66 of Fischer in which the effect of the free-drug methotrexate (MTX), the free-carrier (Pen) or the drug-carrier combination (MTX-Pen; Example 36) were tested for their effect upon cell viability. Table 1 shows that by Days 3 and 4 of testing, not only do MTX and MTX-Pen perform very similarly at higher doses, MTX results in significantly more cell death at lower concentrations in HaCaT cells. The data in Tables 2 and 3 confirm this conclusion for both HaCaT and HT29 cells. Fischer thus teaches that the drug-carrier combination is less effective at inducing cell death than the free-drug alone.

The data provided in Table 6 of Fischer (see pages 72-73) further serves to teach that a drug-linker-carrier compound offers no advantage over a free-drug. Inspection of the IC50 data in Table 6 shows that free paclitaxel reduces cell viability in breast and lung cancer cells more quickly than and at a lower dosage than a paclitaxel-succinyl type linker-carrier compound (Example 43). Table 7 of Fischer (Example 44; see pages 73-74) reports upon the effect of various paclitaxel-succinyl type linker-carrier compounds upon cytotoxicity of different cell lines. After 96 hours, the IC50 for free paclitaxel is considerably reduced compared to the paclitaxel-succinyl type linker-carrier compounds. For example, the IC50 for free paclitaxel is <0.0025 uM in HT29 cells while that of the 2'paclitaxel-succinyl type linker-carrier compound is 0.092 uM and that of the 7'paclitaxel-succinyl type linker-carrier compound is 2.25 uM.

Fischer's demonstration that free-drugs are more efficacious than drug-carrier or drug-succinyl type linker-carrier combinations teaches away from Applicants' compounds prepared according to claim 1. This defect of Fischer is not cured by Schally as Schally also demonstrates that doxorubicin linked with LHRH shows no significant improvement over or performs in an inferior manner than free doxorubicin (see Table 18-1, page 34). Applicants submit that there would be no motivation to combine the LHRH, somatostatin or bombesin analogs of Schally with the linkers of Fischer as Fischer shows that succinyl-type linkers detract from the efficacy of drug-carrier combinations. In addition, neither reference teaches or suggests the inclusion of

Aepa or Doc moieties as a portion of any linker nor does either reference teach or suggest the requirement that molecules prepared with doxorubicin must also include Aepa or Doc.

Applicant respectfully submits that the Examiner has failed to meet the basic CAFC requirement that an obviousness rejection be supported by some suggestion in the prior art to create the claimed invention: [A] proper analysis under §103 requires, *inter alia*, consideration of . . . whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed invention, *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Secondly, as further detailed by the CAFC a "proper obviousness analysis requires consideration of whether the prior art would also have revealed that in so making or carrying out [the claimed invention], those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Thirdly, as recited in the MPEP at 2143.03, "to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F2.d 981, 180 USPQ 580 (CCPA 1974)".

Applicants submit that Fischer's teaching that paclitaxel-succinyl type linker-carrier compounds and Schally's teaching that doxorubicin-LHRH compounds are less efficacious than free-drug or drug-carrier combinations teach away from preparing and expecting success with the compounds of instant claim 1. Applicants also submit that as Fischer and Schally are silent as to the inclusion of Aepa and/or Doc moieties in compounds comprising a doxorubicin or doxorubicin derivatives, these references fail to teach or suggest all aspects of the claims.

4D) Request for the removal of the rejection of claims 1-8, 10-13 and 20 under 35 U.S.C. 103(a)

Applicants respectfully submit that claims 1-8, 10-13 and 20 are not obvious in light of Fischer and Schally. Applicants respectfully request the withdrawal of the rejection of claims 1-8, 10-13 and 20 under 35 U.S.C., 103(a).

Consideration and allowance of all pending claims are respectfully requested.

Examiner Kosar is invited to telephone Applicants' undersigned attorney to facilitate prosecution of this application, if deemed necessary.

Respectfully submitted,

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The undersigned hereby certifies that this correspondence and accompanying documents are being electronically submitted to the U.S. Patent Office under 37 C.F.R. §1.8 on **March 3, 2010**.

/Michael R. Wesolowski/

Michael R. Wesolowski